Rejection under 35 USC §103

Claims 17-20 stand rejected under 35 USC §103(a) as being unpatentable over Samo et al. Samo allegedly teaches a dose of 40 x 10^6 units of interferon and, thus, provides the motivation to make the claimed composition. Additionally, claims 6, 13 and 21-33 stand rejected under 35 USC §103(a) as being unpatentable over Cummins et al. Cummins allegedly teaches the oromucosal administration of interferon for treating neoplastic disease and, thus, provides the motivation for the claimed methods and compositions. Applicant respectfully disagrees for the reasons set forth in the Amendment pursuant to 37 CFR §1.116 filed March 8, 1999. The present supplemental response provides further clarification and addresses the Examiner's request for a side-by-side showing.

Rejection under 35 USC §103 of claims 17-20

As presented in the response filed March 8, 1999, the Samo *et al.* reference fails to render obvious the claimed composition because high dose compositions are neither taught nor suggested by Samo. Samo teaches the administration of interferon for the treatment of a viral condition. As noted in Applicants October 27, 1998 response Samo administers 40 x 10^6 *units* of interferon. However, a unit of interferon is not the same as International Unit. A unit is routinely defined as about one-tenth the quantity of interferon represented by one International Unit. See, for example, Cummins patent 5,019,382, Col. 3, lines 45 - 55. Thus, the actual dose of interferon administered by Samo is 4 x 10^6 IU, a significantly lower dose composition than the presently claimed composition. This teaching does not suggest

an ultra-high dose interferon composition as presently claimed. The Examiner has cited no art which would lead a skilled person to prepare a high dose composition. **There is no suggestion in Samo that an ultra-high dose composition is desirable.**

Rejection under 35 USC §103 of Claims 6, 13 and 21-33

The Cummins reference teaches an anti-neoplastic use for IFN at a dose which is far less than that claimed in the instant application. **There is no teaching or suggestion in Cummins that an 10,000 fold increase in dose would be desirable, or even tolerable, in the treatment of a neoplastic condition.**

The Examiner has requested that a side-by-side comparison be presented. The present application claims priority to, and incorporates by reference, Australian Provisional Patent Application No. PN 9765. In a study (Example 2) reported in that application, none of the mice inoculated with Friend Leukaemia cells and treated with 100 or 1,000 IU of IFN-α survived, while at a dose of 10,000 IU 10-20% of the animals were considered to be cured.

Figure 1A (attached) shows the effect of oromucosal administration of IFN-α on the survival of mice injected with the highly metastatic Friend erythroleukemia cells (FLC) using different doses and excipients. **The highest dose administered to the mice was 10^4 IU which corresponds to a dose of about 240 million IU in humans.**

Figure 1B shows the results of a similar experiment using recombinant human IFN-α 1-8. The highest dose of IFN tested (10^4 IU) was found to be the most effective for both

types of IFN used in the study. As can be seen in the graphs presented, **the mean survival time was significantly increased at a dose of 10^4 IU in these experiments**, irrespective of the excipient used. Indeed, some ultra-high dose IFN-treated mice can be considered to be cured, as they were still alive more than 100 days after inoculation with 100,000 FLC, in a system in which 4 to 5 FLC are sufficient to kill an animal. Mice receiving 10^4 IU had a mean survival time of about 17-19 days, and mice receiving 10^3 IU (equivalent to 24 million IU in humans) survived about 12-13 days, while mice receiving the lowest dose (100 IU, equivalent to 2.4 million IU) had survival times that were minimally increased. It should be noted that, Cummins teaches a dose (about 11 IU/kg) lower than the lowest dose used in these experiments. Thus, **this data convincingly demonstrate that the oromucosal administration of high IFN doses provides superior effectiveness than lower IFN doses.**

Furthermore, the parenteral administration of the ultra-high doses of interferon used in the present invention is known in the art to induce pathological changes. Such pathological changes include changes in blood chemistry, such as leukopenia, bone marrow depression, or other histological parameters. See page 14 of the instant application. Unlike parenteral administration, no consistent effect was observed on any of the hematological or blood chemistry parameters monitored during oromucosal IFN therapy, even in animals treated with up to 100,000 IU of IFN-α. See page 33, lines 13-16. The low level of leukopenia, and absence of detectable myleosuppression, observed in animals treated by the oromucosal route with a dose of interferon which caused a marked bone marrow suppression in animals when administered systemically, suggest that ultra-high doses of type I interferons can be administered by the oral

route without dose limiting myelosuppression. Thus, **the present invention allows the administration of ultra-high interferon doses without the severe and intolerable side effects seen with parenteral interferon administration.**

Conclusion

The instant invention is drawn to compositions and methods of use of ultra-high doses of interferon in the treatment of neoplastic disease. The cited art fails to suggest or teach such a use of ultra-high dose oromucosal interferon or even such an ultra-high dose interferon composition for any purpose. Additionally, an ultra-high dose of IFN has been shown to be more efficacious than low doses of IFN in the treatment of a neoplastic condition. See enclosed Figures. For the reasons previously presented and those presented herein, all rejections having been addressed, reconsideration of the application and an indication of allowability of Claim 6, 13, and 17 - 33 are earnestly solicited.

Respectfully submitted,

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